

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

DECLARATION OF DR. YITZHAK PILPEL UNDER 37 C.F.R. § 1.132

I, Yitzhak Pilpel (Ph.D.), hereby declare as follows:

1. I am currently employed as a faculty member at the Department of Molecular Genetics of the Weizmann Institute, Israel. A true and correct copy of my *Curriculum Vitae* is attached to this declaration as Exhibit A. I am an author of [34 peer-reviewed scientific publications, of which 2 are related to microRNAs ("miRNAs"). I have supervised at least 3 experiments relating to microRNAs including computational mining of the mammalian microRNA repertoire, and experimental analyses of the regulatory agents controlling microRNAs.
2. A nucleic acid sequence of length 18-25 (endogenous or synthetic), which is predicted by a microRNA target algorithm, to bind to the 3' UTR of a mRNA in a manner characteristic of miRNA:mRNA binding, when co-expressed with the target mRNA (such as in an in vitro reporter gene assay), is likely to inhibit expression of the protein encoded by that mRNA.
3. Binding of microRNA to mRNA is characterized by a) 5'-end 'seed' (full complementary between the first 1-8 base pairs of the 5' of a miR and its target), conserved, often flanked by adenosines; b) Compensatory 3'-end in cases in which there is insufficient base-pairing of the microRNA 5' seed; and c) Multiple binding sites on the same mRNA targets which are not obligatory but enhance the binding effect on target repression. The above characteristics were described by various publications, including: Lai and Starck (Nat Genet, 2002; PLoS Biol., 2003), Doench and Sharp (Genes Dev., 2004), Lai (Genome Biol., 2004), Vella et al. (Chem. Biol., 2004) and Brennecke et al. (PLoS Biol., 2005)
4. The effectiveness of microRNA targets prediction algorithms that are based on the above characteristics has been described by numerous studies. As an example, Lewis et al. (Cell 2003), reported a microRNA target prediction algorithm, TargetScan, which is based on the above mentioned characteristics, and have biologically validated 11 out of 15 predicted targets tested, estimating the algorithm's false positive rate to be between 22 and 31 percent. Another algorithm, called miRanda (Enright et al., Genome Biol. 2003), correctly recovered 9 out of 10 biologically validated targets, with an estimated 24-39% false positive rate.
5. **Table A** below provides a list of characteristic nucleic-acid-sequences:mRNA bindings, taken from Rosetta Genomics' patent applications. These nucleic acid sequences exhibit the characteristics of miRNA:mRNA bindings described above, and therefore are likely to inhibit their respective targets when co-expressed (such as in an in vitro reporter gene assay). Indeed, nearly all of the listed bindings are similarly detected by the above mentioned TargetScan algorithm, and half of them are further either detected by the miRanda algorithm, and/or are evolutionarily conserved.




6. It is my opinion that each sequence in column A would likely inhibit the expression of a protein encoded by the target gene in column B in view of the characteristics of miRNA-mRNA binding described above in paragraph 3.
7. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent application relying on this declaration or any patent issuing thereon.

Dated 1/09/08 -- By Tzochi Pirel







Exhibit A


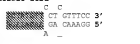
CV

Table A:

Column A	Column B	Column C	Column D	E	F	G
Nucleic acid sequence	Nucleic-acid:target-gene binding site scheme (): the seed region at 5' of the binding nucleic acid)	Supportive data from patent application regarding nucleic-acid's and target-gene's utility	Supportive data from current literature & Rosetta Genomics studies	TargetScan ⁺ target conservation	TargetScan ⁺ miRbase ⁺	
<p>TAGGTAGTTTCCTGTTGTTGGG</p> <p>Sanger name: hsa-miR-196b</p> <p>(Filed in US patent application no. 10/707,147)</p>	<p>Nucleic-acid</p> <p>5'  3'</p> <p>Target gene</p> <p>17/22 complementary base pairs</p> <p>Table 4 (lines 111217-111221)</p> <p>Target/seqID: L38FPL2/6663</p> <p>Nucleic acid seqID/GAM: 354/7553</p>	<p>Pages 180513-81163 paragraphs 51160-81163</p> <p>"Another function of GANM753 is to derivate inhibition of MIN12.3 (Accession NP_000748.1). Accordingly, values of GANM753 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MIN12.3. MIN12.3 (Accession NP_000001.1) is another GANM753 target gene, herein designated TARGET GENE. MIN12.3 BINDING SITE is a target binding site based on the 3' untranslated region of multiple transcripts of mRNA encoded by MIN12.3 corresponding to a target binding site including BINDING SITE 1, BINDING SITE II or BINDING SITE III of Fig. 6. Table 4 illustrates the complementarity of the nucleotide sequences of MIN12.3 BINDING SITE, designated SEQID 5708, to the nucleotide sequence of GANM753 RNA, herein designated GANM RNA, also designated SEQ ID 354. Another function of GANM753 is to derivate inhibition of MIN12.3 (Accession NP_000001.1). Accordingly, values of GANM753 include diagnosis, prevention and treatment of diseases and clinical conditions associated with MIN12.3."</p>		+	+	+
<p>CTAGACTGAAGCTCCTTGAGGA</p> <p>Sanger name: hsa-miR-151</p> <p>(Filed in US patent application no. 10/708,204)</p>	<p>Nucleic-acid</p> <p>5'  3'</p> <p>Target gene</p> <p>18/22 complementary base pairs</p> <p>Table 7 (lines 1488-1492)</p> <p>Target/seqID: SERPINA3/5331</p> <p>Nucleic acid seqID/GAM: 15/1032</p>	<p>Table 8 (lines 7222-7243)</p> <p>"Another function of GANM033 is to derivate inhibition of SERPINA3, a GANM033 target gene which is a member of the serpin family of acute phase inhibitors and therefore is associated with Alzheimer. Accordingly, values of GANM033 include diagnosis, prevention and treatment of Alzheimer, and of other diseases and clinical conditions associated with SERPINA3. The function of SERPINA3 has been established by previous studies. Alpha-1 antitrypsin is a plasma protein inhibitor synthesized in the liver. It is a single glycoprotein chain of about 60,000 daltons and belongs to the class of ester protein inhibitors. In man, the normal zymoz level is about one-tenth that of alpha-1 antitrypsin (H. M'Kinnon, with which there is shared nucleic acid and protein sequence homology (Chaudhri et al. 1987). Both are major acute phase reactants; their concentrations in plasma increase in response to trauma, surgery, and infection. Antithrombin III, which also is structurally similar to alpha-1 antitrypsin, shares little sequence homology to antitrypsinogen and is not an acute phase reactant. Kickey et al. (1981) cloned and analyzed the AACT gene, partly because of the possibility that genetic variation in other protein inhibitors may influence the progress of AAT deficiency. They isolated the AACT gene on a series of cDNA clones, with restriction mapping of about 70 kb around the gene."</p>	<p>a. SERPINA3 mRNA levels are increased in schizophrenia factor et al (Smeets et al. BMC Psychiatry 2007)</p> <p>b. Rosetta Genomics hsa-miR-151 is highly expressed in a variety of tumors.</p>			

<p>AAAGTCTCTCTTTGGTGGGT</p> <p>Sanger name: hsa-miR-520d</p> <p>(Filed in US patent application no. 10/708,951)</p>	<p>Nucleic acid</p> <p>5' C A C A 3'</p> <p>3' G T G T</p> <p>TS G S TTTCTT</p> <p>Nucleic acid</p> <p>21/22 complementary base pairs</p> <p>Table 7 (lines 26274 - 26282)</p> <p>Target/seqID: MIC/A23420.24238</p> <p>Nucleic acid seqID/GAM:1485/338499</p>	<p>Table 8 (80406 - 80439):</p> <p>"A function of GANET849 is described inhibition of MICA, a GANET849 human target gene which encodes for a protein that binds to the receptors on T-cells and NK-cells, activating cytotoxic response, induced by cytotoxic stress and has been MICA is associated with Mycobacterium avium subsp. Paratuberculosis, Mycobacterium bovis subsp. bovis AF131397 and Mycobacterium tuberculosis CDC1551 infections, and therefore GANET849 is associated with the aforementioned infections, as part of a host response mechanism. Accordingly, inhibition of GANET849 as a host diagnosis, prevention and treatment of Mycobacterium avium subsp. paratuberculosis, Mycobacterium bovis subsp. bovis AF131397 and Mycobacterium tuberculosis CDC1551 infections and associated clinical conditions. The function of MICA, and its association with various diseases and clinical conditions has been established by previous studies, as described hereinafter with reference to GANET849."</p>	<p>+</p> <p>α MICA is a target gene of hsa-miR-520d which has the same "seed" as hsa-miR-520d (Lian et al., 2008)</p> <p>β Rostom Gromova: the expression of miR-520d is significantly decreased in lung cancer</p>
<p>AGAAAATGCTCCCTTTGGTGA</p> <p>Sanger name: hsa-miR-527*</p> <p>(Filed in US patent application no. 10/708,953)</p>	<p>Target gene</p> <p>5' AC A G 3'</p> <p>3' TS T C</p> <p>AG GT CCTTC</p> <p>Nucleic acid</p> <p>12/22 complementary base pairs</p> <p>Table 7 (lines 100-105)</p> <p>Target/seqID:SR.Y/1734694</p> <p>Nucleic acid seqID/GAM:8385/345997</p>	<p>Table 8 (lines 490350-490370)</p> <p>"The determining region Y (nucleic determining factor) (ERY, Accession F06, 000146) is a member GANET849 target gene encoded by the human genome. SRY BINDING SITE is a human target binding site located on the 3' untranslated region of cdk19A, controlled by SRY, corresponding to a target binding site such as BINDING SITE 1, BINDING SITE 2 or BINDING SITE 3 of Fig 3. Nucleotide sequences of SRY BINDING SITE, and secondary structure complementary to the nucleotide sequence of GANET849/RYA, are set forth in Tables 6-7, hereby incorporated herein. Another function of GANET849/RYA is described inhibition of SRY, a GANET849/RYA human target gene which is associated with male sex determination. SRY is associated with Turner's syndrome, Down's, and therefore GANET849/RYA is associated with the aforementioned disease. Accordingly, inhibition of GANET849/RYA and of other diseases and clinical conditions associated with SRY."</p>	<p>+</p> <p>Rostom Gromova: hsa-miR-527* is expressed in a variety of tissues.</p>
<p>CACGACACACTGTGGTTGTA</p> <p>Sanger name: hsa-miR-497</p> <p>(Filed in US patent application no. 10/709,691)</p>	<p>Target gene</p> <p>5' CA CCA 3'</p> <p>3' GT GGT</p> <p>AT TT GTGAC</p> <p>Nucleic acid</p> <p>13/22 complementary base pairs</p> <p>Table 7, A (lines 15144-15148)</p> <p>Target/seqID:MGAT5/1810388</p> <p>Nucleic acid seqID/GAM:348/333678</p>	<p>Table 8, a (lines 34080-34165)</p> <p>"Another function of GANET3678 is to inhibit MGAT5, a GANET3678 human target gene which encodes an enzyme that catalyzes beta 1-4 branching on N-linked oligosaccharides. MGAT5 is associated with Schachter's glycosaminoglycan 17/3 infection, and therefore GANET3678 is associated with the aforementioned infection, as part of a host response mechanism. Accordingly, the inhibition of GANET3678 includes the diagnosis, prevention and treatment of 17/3 infection and associated clinical conditions and associated clinical conditions. The function of MGAT5 and its association with various diseases and clinical conditions has been established by previous studies, as described hereinafter with reference to GANET3678."</p>	<p>+</p> <p>Rostom Gromova: miR-497 is highly expressed in brain, prostate, kidney and thyroid.</p>

<p>TCACCAAGTCTAGTTTGTAGAG</p> <p>Sanger name: hcmv-miR U122A*</p> <p>(Filed in US patent application no. 10/707,003)</p>	<p>Nucleic-acid</p> <p>5'  3'</p> <p>3'  5'</p> <p>Target gene</p> <p>14/24 complementary base pairs</p> <p>Table 2 (Lines 54353-54357)</p> <p>Target seq ID: AKAP7711253</p> <p>Nucleic acid seq ID: GAM:3588/577</p>	<p>Pages 17094-17095, paragraph 33328-33329</p> <p>"A Kaposi (FRA) Anchor Protein 7 (AKAP7, Accession NM_004843) is another VGAM77 host target gene. AKAP7 BINDING SITE I through AKAP7 BINDING SITE I are HOST TARGET binding sites found in non-coding regions of miRNA, mediated by AKAP7, corresponding to HOST TARGET binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III. Table 3 illustrates the complementarity of the nucleotide sequences of AKAP7 BINDING SITE I through AKAP7 BINDING SITE I, designated SEQ ID 11253, SEQ ID 11536 and SEQ ID 11806 respectively, to the nucleotide sequence of VGAM77 RNA, herein designated VGAM77 RNA, also designated SEQ ID 1388. Another function of VGAM77 is the inhibition of a Kaposi (FRA) Anchor Protein 7 (AKAP7, Accession NM_004843). Accordingly, utilities of VGAM77 include: diagnosis, prevention and treatment of diseases and clinical conditions associated with AKAP7."</p>	<p>+</p>
<p>CGCACCAGTCTACCAAGGTGT</p> <p>Sanger name: sbv-miR-BART3</p> <p>Filed in US patent application no. 10/708,952</p>	<p>Target gene</p> <p>5'  3'</p> <p>3'  5'</p> <p>Nucleic-acid</p> <p>16/22 complementary base pairs</p> <p>Table 7 (Lines 84412 - 84415)</p> <p>Target seq ID: NP_009961</p> <p>Nucleic acid seq ID: VGAM:14051/351387</p>	<p>Table 8 Lines 2025078-2025094</p> <p>"NP_009961 gene BINDING SITE I and NP_009961 gene BINDING SITE I are host target binding sites found in non-coding regions of miRNA, mediated by NP_009961 gene, corresponding to target binding sites such as BINDING SITE I, BINDING SITE II or BINDING SITE III of Fig 1. Nucleotide sequences of NP_009961 gene BINDING SITE I and NP_009961 gene BINDING SITE I, and secondary structure complementarity to the nucleotide sequence of GAGC13187 RNA are set forth in Table 6." Another function of VGAM77 is the inhibition of a Kaposi (FRA) Anchor Protein 7 (AKAP7, Accession NM_004843). Accordingly, utilities of VGAM77 include: diagnosis, prevention and treatment of diseases and clinical conditions associated with AKAP7."</p>	<p></p>
<p>TCTCTGGTAGCAGATCTGAGC*</p> <p>(Filed in US patent application no. 10/604,945)</p>	<p>Nucleic-acid</p> <p>5'  3'</p> <p>3'  5'</p> <p>Target gene</p> <p>17/22 complementary base pairs</p> <p>Table 2 (Lines 35003-35007)</p> <p>Target seq ID: SF3B3 29681</p> <p>Nucleic acid seq ID: GAM:5264/191</p>	<p>The utilities of the nucleic acid are depicted in detail in Pages 4031-4031, paragraphs 30031-30036.</p> <p>The following utility is taken from the present invention:</p> <p>"It is further appreciated that a function of VGAM77 is the inhibition of expression of host target genes, as part of a novel viral mechanism of attaching a host. Accordingly, utilities of VGAM77 include: diagnosis, prevention and treatment of viral infections by Human immunodeficiency virus 1.</p> <p>Specific functions, and accordingly utilities, of VGAM77 include: with, and may be defined from, the identity of the host target genes which VGAM77 binds and inhibits, and the function of these host target genes, as elaborated herein below."</p>	<p>Reuter Oronson biologically validated the miR</p> <p>+</p>

<p>TGCTATTTCGGCTGCCAGAGTGC*</p> <p>(Filed in US patent application no.10/604,943)</p>	<p>Nucleic-acid</p>  <p>Target gene</p> <p>20/22 complementary base pairs</p> <p>Table 2(Lines 7363-7367) TargetSeqID:INH6A/904 Nucleic acid seqID:VGAM480/145</p>	<p>Page 830 paragraphs 1993</p> <p>"It is yet further appreciated that a function of VGAM4145 is inhibition of expression of host target genes, as part of a novel viral mechanism of attaching a host. Accordingly, inhibition of VGAM4145 nucleic acid diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM4145 nucleic acid, and may be deduced from, the identity of the host target genes which VGAM4145 binds, and inhibits, and the functions of these host target genes, as elucidated herein below."</p> <p>Paragraph 2141 recites the VOR396 utility, which recites an "open up like" cluster of novel viral genes RNA. Recites, including VGAM1440</p> <p>"It is appreciated that a function of VOR396 gene, herein designated VOR GENE, is inhibition of expression of host target genes, as part of a novel viral mechanism of attaching a host. Accordingly, inhibition of VOR396 gene nucleic acid diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VOR396 gene nucleic acid, and may be deduced from, the identity of the host target genes, which are inhibited by VGAM1440, comprised as the "open up like" cluster of VOR396 gene VGAM143 host target genes, VGAM143 host target protein, VGAM144 host target protein, VGAM145 host target protein, VGAM146 host target protein and VGAM147 host target protein, herein schematically represented by VGAM143 HOST TARGET PROTEIN through VGAM147 HOST TARGET PROTEIN. The functions of these host target genes is elucidated herein below with reference to VGAM143, VGAM145, VGAM146, VGAM143, VGAM146 and VGAM147. Fig. 9 further provides a conceptual description of novel heteromultimerically detected regulatory viral genes, referred to here as Viral Genes: Recard 396 (VOR396) and gene, which recites an "open up like" cluster of novel viral genes RNA. Recites, each of which has modulates expression of at least one host target gene, the function and utility of which at least one host target gene is known as the: at "</p>	<p>Reverts Genomics validated this nucleic acid by Real Time PCR</p> <p>+</p> <p>+</p>
<p>TCATAGTTCCTCGTTTCCTGTAT*</p> <p>(Filed in US patent application no.10/604,943)</p>	<p>Nucleic-acid</p>  <p>Target gene</p> <p>16/22 complementary base pairs</p> <p>Table 2(Lines 7428-7432) TargetSeqID:ZNF363627 Nucleic acid seqID:VGAM482/147</p>	<p>Page 842 paragraphs 2021</p> <p>"It is yet further appreciated that a function of VGAM4147 is inhibition of expression of host target genes, as part of a novel viral mechanism of attaching a host. Accordingly, inhibition of VGAM4147 nucleic acid diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VGAM4147 nucleic acid, and may be deduced from, the identity of the host target genes which VGAM4147 binds, and inhibits, and the functions of these host target genes, as elucidated herein below."</p> <p>Paragraph 2241 recites the VOR396 utility, which recites an "open up like" cluster of novel viral genes RNA. Recites, including VGAM1442</p> <p>"It is appreciated that a function of VOR396 gene, herein designated VOR GENE, is inhibition of expression of host target genes, as part of a novel viral mechanism of attaching a host. Accordingly, inhibition of VOR396 gene nucleic acid diagnosis, prevention and treatment of viral infection by Vaccinia Virus. Specific functions, and accordingly utilities, of VOR396 gene nucleic acid, and may be deduced from, the identity of the host target genes, which are inhibited by VGAM1442, comprised as the "open up like" cluster of VOR396 gene VGAM143 host target genes, VGAM143 host target protein, VGAM144 host target protein, VGAM145 host target protein, VGAM146 host target protein and VGAM147 host target protein, herein schematically represented by VGAM143 HOST TARGET PROTEIN through VGAM147 HOST TARGET PROTEIN. The functions of these host target genes is elucidated herein below with reference to VGAM143, VGAM145, VGAM146, VGAM143, VGAM146 and VGAM147. Fig. 9 further provides a conceptual description of novel heteromultimerically detected regulatory viral genes, referred to here as Viral Genes: Recard 396 (VOR396) and gene, which recites an "open up like" cluster of novel viral genes RNA. Recites, each of which has modulates expression of at least one host target gene, the function and utility of which at least one host target gene is known as the: at "</p>	<p>Reverts Genomics validated this nucleic acid by Real Time PCR</p> <p>+</p> <p></p>

		<p>as the "open-like" cluster of VOR389 gene, VQAM143 host target protein, VQAM143 host target protein, VQAM144 host target protein, VQAM145 host target protein, VQAM146 host target protein and VQAM147 host target protein, herein schematically represented by VQAM1 HOST TARGET PROTEIN through VQAM1 HOST TARGET PROTEIN. The function of these host target genes is elucidated hereinafter with reference to VQAM143, VQAM145, VQAM144, VQAM145, VQAM146 and VQAM147. Fig. 9 further provides a conceptual description of novel biochemically detected regulatory viral gene, referred to here as Viral Genome Record 390(VOR390) viral gene, which encodes an "open-like" cluster of novel viral-micro RNA-like genes, each of which as non-modifiable expression of at least one host target gene, the function and utility of which at least one host target gene is known in the art."</p>		
<p>CGCCTTATTTCACATTAGATGG*</p> <p>(Filed in US patent application no.10/604,943)</p>	<p>Nucleic-acid</p> <p>5' TOCA AT GATGG 3'</p> <p>3' AGGT TA CTACC 5'</p> <p>Target gene</p> <p>20/22 complementary base pairs</p> <p>Table 2(Lines 7203-7207) Target:seqID:ACADSB/838 Nucleic acid seqID:VGAM-477(142)</p>	<p>Page 813, paragraph 1952</p> <p>"It is yet further appreciated that a function of VQAM143 is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, inhibition of VQAM143 includes diagnosis, prevention and treatment of viral infection by Vircana Virus. Specific functions, and accordingly inhibition, of VQAM143 coordinate with, and may be deduced from, the identity of the host target genes which VQAM143 binds and inhibits, and the function of these host target genes, as elucidated herein below."</p> <p>Paragraph 1953 recites the VOR390 utility, which encodes an "open-like" cluster of novel viral micro RNA-like genes, including VQAM 144</p> <p>"It is appreciated that a function of VOR390 gene, herein designated VOR GENE, is inhibition of expression of host target genes, as part of a novel viral mechanism of attacking a host. Accordingly, inhibition of VOR390 gene includes diagnosis, prevention and treatment of viral infection by Vircana Virus. Specific functions, and accordingly inhibition, of VOR390 gene coordinate with, and may be deduced from, the identity of the host target genes, which are inhibited by VQAM143 as compared to the "open-like" cluster of VOR389 gene. VQAM143 host target protein, VQAM143 host target protein, VQAM144 host target protein, VQAM145 host target protein, VQAM146 host target protein and VQAM147 host target protein, herein schematically represented by VQAM1 HOST TARGET PROTEIN through VQAM1 HOST TARGET PROTEIN. The function of these host target genes is elucidated hereinafter with reference to VQAM143, VQAM145, VQAM144, VQAM145, VQAM146 and VQAM147. Fig. 9 further provides a conceptual description of novel biochemically detected regulatory viral gene, referred to here as Viral Genome Record 390(VOR390) viral gene, which encodes an "open-like" cluster of novel viral-micro RNA-like genes, each of which as non-modifiable expression of at least one host target gene, the function and utility of which at least one host target gene is known in the art."</p>	*	*

* These sequences are not depicted in Sanger 10.0 database.

¹ TS = TargetScan (version 4.0)

² Target conserv. = Target conservation ≥ 2 organisms

³ nR = nRanda (2003)

Curriculum Vitae

Yitzhak Pilpel

A: Personal Details

Date of birth: 12/9/1968
Place of birth: Jerusalem, Israel
Marital status: Married + 3 children
Military service: Four years' service in the IDF
Citizenship: Israeli
Mailing Address:
Dept. of Molecular Genetics
Weizmann Institute of Science
Rehovot 76100, Israel
Contact Information:
Phone: 972 8 934 6058
Fax: 972 8 934 4108
E-mail: pilpel@weizmann.ac.il
Lab home page: <http://longitude.weizmann.ac.il>

B: Education

- 2000 - 2002 Postdoctoral Fellow. Department of Genetics, Harvard Medical School, Boston, MA, USA. Advisor: Prof. George M. Church.
- 1995 - 1999 Ph.D. degree. Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel. Thesis title: Structural and evolutionary genomics of molecular recognition repertoires. Advisors: Prof. Doron Lancet; Prof. Ephraim Katchalski-Katzir.
- 1994 - 1995 Studies toward M.Sc. degree; transfer to direct Ph.D. track. Department of Membrane Research and Biophysics, Weizmann Institute of Science, Rehovot, Israel. Advisors: Prof. Doron Lancet; Prof. Ephraim Katchalski-Katzir.
- 1990 - 1993 B.Sc. degree. Major: Biology. Tel-Aviv University, Tel-Aviv, Israel.

C: Employment History

- 2003 - present Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel. Senior Scientist, group leader.
Incumbent of the Aser Rothstein Career Development Chair of Genetic Diseases.

D: Academic Administration

- 2004 - present Feinberg Graduate School, Weizmann Institute of Science, Rehovot, Israel. Head of the Graduate Program in Bioinformatics.

E. Other Appointments

• Positions in academia and membership on committees

- 2007 - present Feinberg Graduate School, Weizmann Institute of Science, Rehovot, Israel. Member of the Board of Studies, Life Sciences.
- 2003-present Head Bioinformatics graduate program at the Feinberg Graduate School, Weizmann Institute of Science, Rehovot, Israel.

• Teaching experience - courses taught

- 2003-2006 Developed and taught the course, "Computational Functional Genomics." Feinberg Graduate School, Weizmann Institute of Science.
- 1998 Teaching Assistant for the course, "Programming for Bioinformatics and Internet." Feinberg Graduate School, Weizmann Institute of Science.
- 1997 Lecturer for the course, "Computational Genomic and Bioinformatics." Feinberg Graduate School, Weizmann Institute of Science.
- 1994 Teaching Assistant for the course, "Receptors and Recognition." Feinberg Graduate School, Weizmann Institute of Science.
- 1992 Teaching Assistant in mathematics for the course, "Introduction to Differential and Integral Calculus." Tel Aviv University.

• Membership on scientific advisory boards, and consulting activities

- Member of the Program Committee, RECOMB Regulatory Genomics 2006, (San Diego CA, USA).
- Member of the Program Committee, RECOMB 2005, (San Diego CA, USA)
- Member of the Program Committee, RECOMB Regulatory Genomics and Systems Biology 2005, (San Diego CA, USA).
- Member of the Program Committee, RECOMB Regulatory Genomics 2004, (San Diego CA, USA).
- 2001 - 2002 Consultant on modeling and structure prediction of G-protein coupled receptors. Pfizer, Inc., Cambridge, MA, USA.

• Membership on editorial boards

- Associate Editor, PLoS Computational Biology
- Associate Editor, Biology Direct

F: International Recognition

• Prizes, awards, and competitive scholarships

- 2007 Levinson Prize in Biology, awarded by the Scientific Council, Weizmann Institute of Science.
- 2006 James Heineman Research Award, (awarded by Minerva Stiftung).
- 2005 EMBO Young Investigator Award, awarded by the European Molecular Biology Organization.
- 2003 Fellowship from the Center for Complexity Sciences – a merit-based fellowship for young Principal Investigators (awarded by the Horowitz Foundation).
- 2002 Fellow of the PhRMA Foundation, a Center for Excellence in Integration of Genomics and Informatics, Harvard University.
- 2000 Fulbright Postdoctoral Award, awarded by the United States - Israel Educational Foundation.
- 1999 Prize of Distinction for outstanding Ph.D. studies. Awarded by the Feinberg Graduate School, Weizmann Institute of Science.
- 1998 First Prize in the National Competition for Multidisciplinary Ph.D. Study. Awarded by the Faculty of Mathematics and Natural Sciences, Hebrew University of Jerusalem.
- 1997 Fellowship of Distinction for outstanding achievement in studies and research. Awarded by the Dean of the Feinberg Graduate School, Weizmann Institute of Science.

• Invited talks at international meetings

1. 2007 The German Bioinformatics Conference, Potsdam, Germany.
2. 2007 The 9th International Northern European Bioinformatics Conference. Umeå, Sweden.
3. 2007 "Comparative genomics of translation efficiency." Guest lecturer in the seminar series, Dept. of Biology, Columbia University, New York, NY, USA.
4. 2007 "Comparative genomics of translation efficiency." Guest lecturer in the seminar series, Dept. of Biological Engineering, MIT, Cambridge, MA, USA.
5. 2006 "Differential gene expression regulation and species divergence." International course on "Global interrogations of biological processes." ISREC, Lausanne, Switzerland.

6. 2006 "Differential gene expression regulation and species divergence." Systems Biology and Evolution Workshop, Imperial College, London, UK.
 7. 2006 "Coping with genetic and non-genetic stress." Baure Center for Genomics Research, Harvard University, Cambridge, MA, USA.
 8. 2006 "Systems biology view of expression regulation." The 6th EMBO Young Investigator Meeting, Vienna, Austria.
 9. 2006 "Coping with genetic and non-genetic perturbations." Guest lecturer in the seminar series of the Rockefeller Center for Studies in Physics and Biology, New York, NY, USA.
 10. 2005 "Responsive backup circuits." The Yeast Systems Biology Network, Gotenburg, Sweden.
 11. 2005 "Coupled sense and anti-sense regulation." The 3rd Bertinoro Computational Biology Meeting, Bertinoro, Italy.
 12. 2005 "Transcription control of genetic backup circuits." EMBO Practical Course on Functional Genomics, Milan, Italy.
 13. 2004 "Revealing the architecture of genetic backup circuits through inspection of transcription regulatory networks." The First Annual RECOMB Meeting on Regulatory Genomics, University of California at San Diego, San Diego, CA, USA.
 14. 2003 "Computational detection and analysis of regulatory SNPs." The 5th International Northern European Bioinformatics Conference, Helsinki, Finland.
 15. 2003 "Promoter sequence and the thermodynamics of DNA-protein interactions." The 2nd Annual McGill Workshop on Computational Biology, Barbados.
 16. 2001 "Computational identification of genetics regulatory networks." DIMACS Workshop on Integration of Diverse Biological Data, Rutgers University, Piscataway, NJ, USA.
- **Invited talks at national meetings**
 1. 2008 "Coping with genetic and non-genetic stress." ILANIT, Eilat, Israel.
 2. 2004 "Promoter analysis of gene duplications reveals the architecture of genetic backup circuits." The Annual Meeting of the Israel Society of Genetics, (Haifa, Israel).
 3. 2003 "Computational dissections of genetics regulatory networks." The 6th Israeli Bioinformatics Conference, Haifa, Israel.
 - **Refereed international conference talks**

1. 2007 "Comparative genomics of translation regulation in yeast," a "Highlight Track" talk. ISMB, (Vienna Austria).
2. 2005 "Genome-wide transcription regulatory circuits controlling cellular malignant transformation." (One of 50 talks selected for oral presentation from 500 submissions. Lecture delivered by my student, since I was unable to attend.) Best Poster Award. ISMB, (Detroit, USA).
3. 2005 "Transcriptional reprogramming in genetic backup circuits." (One of 50 talks selected for oral presentation from 500 submissions. Lecture delivered by my student, since I was unable to attend.) ISMB, (Detroit, USA).
4. 2005 "Characterization of the effects of TF binding site variations on gene expression: Towards predicting the functional outcomes of regulatory SNPs." (Lecture delivered by my student.) RECOMB Regulatory Genomics and Systems Biology, (San Diego, USA).
5. 2005 "Backup by paralogs decouples genes lethality from centrality: evidence for preferential backup of hubs." RECOMB Regulatory Genomics and Systems Biology, (San Diego, USA).
6. 2005 "Phenotypic divergence correlates with translational control signals in protein coding sequences in yeast species." (Lecture delivered by my student.) RECOMB Regulatory Genomics and Systems Biology (San Diego, USA).

G: Scientific Productivity

- **Competitive national and international grants (latest grant first)**
 - 2008 - 2012 "Expression regulatory networks: Beyond promoters and transcription control." European Research Foundation (ERC) "Ideas Grant," a personal competitive grant awarded by the EU. €1,300,000.
 - 2004-present A non-competitive grant from the Ben May Foundation. \$105,000.
 - 2007 - 2009 "Systems biology of regulatory networks." Minerva Foundation. €150,000.
 - 2007 - 2008 "A potential role for non-coding RNA in regulating gene expression noise: a mathematical approach" (with T. Tlustý), Clore Center for Biological Physics, Weizmann Institute of Science. \$20,000.
 - 2006 - 2010 "Evolutionary Conditioning," a non-competitive grant from the Tauber Foundation (with N. Eshel Ben-Jacob, et al.). \$200,000.
 - 2006 - 2010 James Heineman Research Award, (awarded Minerva Stiftung) €60,000.
 - 2006 - 2009 EMBO Young Investigator Award. European Molecular Biology Organization. €45,000.

- 2005 - 2010 "The effect of mutations on transcription regulation." European Union Network of Excellence in Bioinformatics. €300,000.
- 2005 Grant from the Center for Systems Biology, Weizmann Institute of Science. \$10,000.
- 2004 - 2007 "Deciphering the structure and logic of genetic regulatory networks and signaling pathways in multi-cellular organisms." Israel Science Foundation. \$240,000.
- 2004 - 2006 "Computational dissections of transcription factor-promoter interactions." Minerva Foundation. €75,000
- 2003 - 2004 Personal grant from the Horowitz Foundation Center for Complexity Sciences. \$88,000.
- **Students, Postdoctoral and Research Fellows**
 - Dr. Itay Furman, 2006 - present. Programmer.
 - Dr. Orna Dahan, 2005 - present. Research Fellow.

Postdoctoral Fellows

- Dr. Naomi Siew, 2006 - present. Postdoctoral Fellow (shared with Prof. Dan Tawfik).
- Dr. Maria Rodriguez Martinez, 2006 - present. Postdoctoral Fellow (shared with Dr. Tsvi Tlusty).

Ph.D. Students

- Ran Kafri, 2003 - 2006. Ph.D. student. (Graduated with Distinction on the Dean's List). Currently a postdoctoral fellow with Prof. Marc Kirschner, Harvard Medical School.
- Michal Lapidot, 2003 - present. Ph.D. student. (Recipient of the Horowitz Foundation Center for Complexity Sciences Award).
- Amir Mitchell, 2004 - present. Ph.D. student.
- Reut Shalgi, 2005 - present. Ph.D. student (shared with Moshe Oren). (Recipient of the Horowitz Foundation Center for Complexity Sciences Award. Recipient of the Lee Segal Award of Mathematical Biology Lee Segal Award for Mathematical Applications to Biological Systems).
- Orna Man, 2005 - 2007. Ph.D. student. (Graduated with distinction; Recipient of the Daniel Brenner Memorial Prize, awarded by the Feinberg Graduate School, Weizmann Institute of Science).
- Ilya Venger, 2005 - present. Ph.D. student (shared with Dr. Asaph Aharoni).
- Ophir Shalem, 2007 - present. Ph.D. student
- Zohar Bloom, 2007 - present. Ph.D. student.

M.Sc. Students

- Reut Shalgi, 2003 - 2005. M.Sc. student (shared with Prof. Ron Shamir).
- Yael Garten, 2003 - 2005. M.Sc. student. Currently Ph.D. student, Stanford University.
- Arren-Bar Even, 2004 - 2006. M.Sc. student (shared with Prof. Naama Barkai). (Graduated with Distinction on the Dean's List). Currently working in industry.
- Ilana Lavie, 2004 - 2006. M.Sc. student (shared with Prof. Ronen Basri).
- Ophir Shalem, 2006 - 2007. M.Sc. student (shared with Dr. Eran Segal).
- Avihu Yona, 2007 - present. M.Sc. student.

• National and international collaborators

National:

- Dr. Asaph Aharoni, Dept. of Plant Sciences, Weizmann Institute of Science
- Prof. Naama Barkai, Dept. of Molecular Genetics, Weizmann Institute of Science
- Prof. Ronen Basri, Dept. of Computer Science and Applied Mathematics, Weizmann Institute of Science
- Prof. Eytan Domany, Dept. of Physics of Complex Systems, Weizmann Institute of Science
- Prof. Moshe Oren, Dept. of Immunology, Weizmann Institute of Science
- Prof. Varda Rotter, Dept. of Molecular Cell Biology, Weizmann Institute of Science
- Dr. Eran Segal, Dept. of Computer Science and Applied Mathematics, Weizmann Institute of Science
- Prof. Dan Tawfik, Dept. of Biological Chemistry, Weizmann Institute of Science

- Prof. Eshel Ben-Jacob, School of Physics and Astronomy, Tel-Aviv University
- Prof. David Horn, School of Physics and Astronomy, Tel-Aviv University
- Prof. Eytan Ruppin, MD, Ph.D., School of Computer Science and School of Medicine, Tel-Aviv University
- Prof. Ron Shamir, School of Computer Science, Tel-Aviv University

International:

- Prof. Duccio Cavalieri, Florence University
- Prof. Craig Hunter, Harvard University
- Prof. Roy Kishony, Harvard University
- Prof. Daniel Segre, Boston University

H: Patents

Provisionary patent application: "Global and local architecture of the mammalian microRNA-transcription factor regulatory network." In preparation by Yeda Research and Development Co., Ltd.

I. Languages

Hebrew: Reading: 3, Writing: 3, Speaking: 3

English: Reading: 3, Writing: 3, Speaking: 3

Scale: 1 (basic) to 3 (fluent)

List of Publications Yitzhak Pilpel

Refereed Articles

29. Kafri R, Dahan O, Levy J & **Pilpel Y**. Preferential genetic backup of hubs in the protein interaction network: evidence for evolutionary selection for redundancy. *Proc Natl Acad Sci U S A* (2008, in press).
28. Lapidot M, Man-Mizrahi O, & **Pilpel Y**. Functional characterization of variations within regulatory motifs. *PLoS Genetics* (2008, in press).
27. Segal L,^{*} Lapidot M,^{*} Solan Z, Ruppin E, **Pilpel Y**, & Horn D. Nucleotide variation of regulatory motifs may lead to distinct expression patterns. *Bioinformatics* 2007 23(13):i440-9 (2007). ***These authors contributed equally to the work.**
26. Shalgi R, Leiber D, Oren M. & **Pilpel Y**. Global and local architecture of the mammalian microRNA-transcription factor regulatory network. *PLoS. Comput. Biol.* 3(7): e131 (2007).
25. Man O & **Pilpel Y**. Phenotypic divergence of yeast species is associated with differential translational efficiency of entire genetic modules. *Nature Genetics* 39(3): 415-421 (2007).
24. Lapidot M & **Pilpel Y**. Genome wide overview of natural antisense transcription --- how is it regulated, how does it regulate. *EMBO report* 7(12): 1216-1222 (2006).
23. Kafri R, Levi M & **Pilpel Y**. The regulatory utilization of genetic redundancy through responsive backup circuits. *Proc Natl Acad Sci U S A* 103(31): 11653-11658 (2006).
22. Xi Y, Shalgi R, Fodstad O, **Pilpel Y**, & Jingfang Ju. Differentially regulated miRNAs and actively translated mRNA transcripts by tumor suppressor p53 in colon cancer. *Clinical Cancer Research* 12(1): 2014-2024 (2006).
21. Bar-Even, A, Paulsson J, Maheshtri N, Carmi M, O'Shea E, **Pilpel Y*** & Barkai N.* Noise in protein expression scales with natural protein abundance. *Nature Genetics* 36(6): 36-43 (2006). ***Corresponding authors.**
20. Nadejda S, Vardy E, Molshanski-Mor S, Eitan A, **Pilpel Y**, Schuldiner S, & Bibi E. 3D model of the *Escherichia coli* multidrug transporter MdfA reveals an essential membrane-embedded positive charge. *Biochemistry* 44(45): 14870-14880 (2005).
19. Shalgi R, Lapidot M, Shamir R & **Pilpel Y**. A catalog of stability-associated sequence elements in 3' UTRs of yeast mRNAs. *Genome Biology* 6(10): R86. (2005).
18. Tabach Y, Milyavsky M, Zuk O, Yitzhaki A, Shats I, Domany, E, Rotter, V & **Pilpel Y**. The promoters of human cell cycle genes integrate signals from two tumor suppressive pathways during cellular transformation. *Molecular Systems Biology* 1: 2005.002 (2005).

17. Kafri R, Bar-Even A. & **Pilpel Y**. Transcription control reprogramming in genetic backup circuits. *Nature Genetics* 37(3):295-299 (2005).
16. Garten Y,* Kaplan S* & **Pilpel Y**. Extraction of Transcription Regulatory Signals from Genome-wide DNA-protein interaction Data. *Nucleic Acids Research* 33(2): 605-615 (2005) ***These authors contributed equally to the work.**
15. Lapidot M & **Pilpel Y**. Comprehensive quantitative analyses of the effects of promoter sequence elements on mRNA transcription. *Nucleic Acid Research* 31: 3824-3828 (2003).
14. Sudarsanam P,* **Pilpel Y*** & Church GM. Genome-wide co-occurrence of promoter elements reveals a *cis*-regulatory cassette of rRNA transcription motifs in *S. cerevisiae*. *Genome Research* 12: 1723-1731 (2002). ***These authors contributed equally to the work.**
13. Zhu Z,* **Pilpel, Y*** & Church GM. Identification of transcription factor binding sites via a Transcription Factor-Centric Clustering (TFCC) algorithm. *J.Mol.Biol.* 318: 71-81 (2002). ***These authors contributed equally to the work.**
12. Cohen B, **Pilpel Y**, Mira R & Church GM. Discrimination between the Yap1p and Yap2p transcriptional networks in yeast. *Mol. Biol. Cell.* 13: 1608-1614 (2002).
11. **Pilpel Y**, Sudarsanam P & Church GM. Identifying regulatory networks by combinatorial analysis of promoter elements. *Nature Genetics* 29: 153-159 (2001).
10. Fuchs T, Glusman G, Horn-Saban S, Lancet D. & **Pilpel Y**. The human olfactory subgenome: from sequence to structure and evolution. *Hum Genet* 108: 1-13 (2001).
9. Lapidot M, **Pilpel Y**, Gilad Y, Falcovitz A, Sharon D, Haaf T. & Lancet D. Mouse-Human Orthology Relationships in an Olfactory Receptor Gene Cluster. *Genomics* 71: 296-306 (2001).
8. Conticello SG, **Pilpel Y**, Glusman G & Fainzilber M. Position-specific codon conservation in hypervariable gene families. *Trends Genet* 16: 57-59 (2000).
7. Glusman G, Bahar A, Sharon D, **Pilpel Y**, White J & Lancet D. The olfactory receptor gene superfamily: data mining, classification, and nomenclature. *Mamm Genome* 11: 1016-1023 (2000).
6. **Pilpel Y**, Ben-Tal N & Lancet D. kPROT: a knowledge-based scale for the propensity of residue orientation in transmembrane segments. Application to membrane protein structure prediction. *J Mol Biol* 294: 921-935 (1999).

5. Sharon D, Glusman G, **Pilpel Y**, Khen M, Gruetzner F, Haaf T. & Lancet D. Primate evolution of an olfactory receptor cluster: diversification by gene conversion and recent emergence of pseudogenes. *Genomics* 61: 24-36 (1999).

4. **Pilpel Y** & Lancet D. The variable and conserved interfaces of modeled olfactory receptor proteins. *Protein Sci* 8: 969-977 (1999).

3. Segre D, Lancet D, Kedem O & **Pilpel Y**. Graded autocatalysis replication domain (GARD): kinetic analysis of self-replication in mutually catalytic sets. *Orig Life Evol Biosph* 28: 501-514 (1998).

2. Segre D, **Pilpel Y** & Lancet D. Mutual catalysis in sets of prebiotic organic molecules: Evolution through computer simulated chemical kinetics. *PhysicaA* 249: 558-564 (1998).

1. Lancet D, Kedem O & **Pilpel Y**. Emergence of order in small autocatalytic sets maintained far from equilibrium: application of a probabilistic receptor affinity distribution (RAD) model. *Ber Bunsenges Phys Chem* 98: 1166-1169 (1994).

Invited Editorials (News & Views)

2. Furman I. & **Pilpel Y**. Promoting mining of human promoters. News & Views in *Molecular Systems Biology* 2: 2006.0030 (2006).

1. **Pilpel Y** & Lancet D. Olfaction. Good reception in fruitfly antennae. News & Views in *Nature* 398: 285-287 (1999).

Book Chapters

1. **Pilpel Y**, Sosinsky A & Lancet D. Molecular biology of olfactory receptors. *Essays Biochem* 33: 93-104 (1998).

Invited Reviews

1. Sharon D, Glusman G, **Pilpel Y**, Horn-Saban S. & Lancet D. Genome dynamics, evolution, and protein modeling in the olfactory receptor gene superfamily. *Ann N Y Acad Sci* 855: 182-193 (1998).

Refereed Conference Proceedings

2. Lapidot M & **Pilpel Y**. Characterization of the Effects of TF Binding Site Variations on Gene Expression. Towards Predicting the Functional Outcomes of Regulatory SNPs. *Lecture Notes in Bioinformatics*, LNBI 4023 Proceedings, Springer-Verlag (2007).

1. Man O, Susman JL. & **Pilpel Y**. Examination of the tRNA Adaptation Index as a Predictor of Protein Expression Levels. *Lecture Notes in Bioinformatics*. LNBI 4023 Proceedings, Springer-Verlag (2007).